REMARKS

In response to the Office Action mailed November 10, 2009, claim 1 has been amended. No claims have been canceled and no new claims have been added. Support for all of the above amendments can be found throughout the as-filed specification and original claims, for example, on pages 70, lines 5-15; page 83, lines 4-8, ad Examples 2 and 3. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1, 4, 8, 11-18, and 20-23 are pending and under examination. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, WRITTEN DESCRIPTION

Claims 1, 4, 6-8, and 10-23 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement because the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Action alleges that the specification does not provide a representative number of cellular adhesion related agents, antibodies or derivatives thereof interacting with a cellular adhesion molecule, or interacting with integrin receptors, that is required to practice the claimed invention.

Applicants respectfully traverse this basis for rejection and submit that the as-filed specification provides ample written description support for the entire breadth of the presently claimed invention.

As an initial point, Applicants, without acquiescence, have amended claim 1 to recite wherein the interaction substance is an antibody or a derivative thereof that binds to an integrin receptor. Applicants respectfully note that this amendment is consistent with the

amendment suggested by the Examiner (see bottom of page 8 of the Office Action).

Applicants respectfully point out that the presently claimed interaction substance is an antibody or a derivative thereof that binds to an integrin receptor. Applicants submit that antibodies that bind to an integrin receptor are exemplified in the as-filed specification, for example, CD49a-f antibodies or CD 29 antibodies (see page 70, lines 17-20 and page 71, line 10-15). Moreover, one having skill in the art could easily generate additional antibodies specific to a given cell adhesion molecule, as the polypeptide sequences of said molecules were known and the methods of making antibodies were well known to those having ordinary skill in the art at the time the instant application was filed. Thus, one having skill in the art would believe Applicants to be in possession of the presently claimed interaction substances at the time the instant application was filed.

Accordingly, Applicants submit that the as-filed specification comports with §112, first paragraph and respectfully request that this basis for rejection be considered and withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. §103(A), FIRST REJECTION

Claims 1, 4, 8, 11-18, 22, and 23 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zou *et al.* (Cancer Gene Therapy, 2000, 7:683-696) in view of Fortunati *et al.* (Gene Therapy, 2000, 7: 1505-1515) and Sugano et al (Cancer Research, 2000, 60: 6942-6949), as evidenced by GIBCO product insert for OPTI-MEM® (Form No. 2017, June 2001, one page) and Kamata *et al.* (J of Biological Chemistry, 1994, 269, 26006-26010). Specifically, the Action alleges that Zou et al teach a composition comprising a liposome complexed to p53 cDNA that is used to enhance the introduction efficiency of the p53 cDNA into cells. The Action further alleges that Zou et al also teach a medium comprising a salt (as evidenced by GIBCO product insert for OPTI-MEM® and that Kamata *et al.* teach the CD29 integrin inherently binds to collagen. However, the Action acknowledges that Zou *et al.* fail to teach a composition comprising antibodies that bind integrin or CD29. The Action relies on the combined teachings of Fortuni *et al.* and Sugano *et al.* to remedy this insufficiency. The Action concludes that it would have been *prima facie* obvious to for one having skill in the art to

combine the reference as suggested in the Action and arrive at the presently claimed invention with a reasonable expectation of success.

Applicants respectfully traverse this basis of rejection and submit that the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention. The Action fails to provide a sufficient basis for one having ordinary skill in the art to predictably arrive at the presently claimed invention with any reasonable expectation of success.

At a minimum, it must be demonstrated that the cited references provide a sufficient basis to predictably arrive at the presently claimed invention, and even assuming, arguendo, that the cited references teach each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex*, Inc., No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). In the instant case, the Action has failed to provide sufficient rationale why one of skill in the art one would motivated to combine Zou *et al.* with Sugano *et al.* and Fortunati *et al.* so as to formulate a composition comprising an integrin receptor antibody that enhances the introduction efficiency of genetic material in a cell and arrive at the presently claimed invention with any reasonable expectation of success.

As an initial note, Applicants, without acquiescence, have amended the claims to recite a composition comprising an interaction substance that is an antibody or a derivative thereof that bind to an integrin receptor, wherein the composition enhances the introduction efficiency of a genetic material (*i.e.*, a target substance) into a cell in a liquid phase or on a solid support. The claimed invention significantly improves transfection efficiency for cells which are traditionally difficult to transfect, PC12 cells and HepG2. Specifically, a 100 fold increase in transfection efficiency was observed (page 110, lines 21-31 and pages 115-116). Further, the claimed invention demonstrates improvements in transfection efficiency in liquid phase and on a solid support (Examples 2 and 3). In contrast, none of the cited references, either alone or in

combination, provide sufficient teachings, suggestions, motivation, or rationale to arrive at the presently claimed invention with any reasonable expectation of success.

Applicants respectfully submit that Zou *et al.* merely teach that "cationic liposomes were generally more effective at transfecting genes than were micelles of the same lipid composition, thus, suggesting a role for the bilayer structure in facilitating transfection. In addition, Zou *et al.* teach that the transfection efficiency of the liposome-delivered genes was highly dependent upon the lipid composition, lipid/DNA ratio, particle size of the liposome-DNA complex, and cell lines used" (see Abstract of Zou *et al.*). As acknowledged by the Examiner, Zou *et al.* fail to teach a composition comprising antibodies that bind integrin or CD29. However, Applicants respectfully note that Zou *et al.* fail to teach any composition comprising any antibody, let alone a composition comprising antibodies that bind an integrin receptor. In addition, Zou *et al.* fail to teach a composition that enhances the introduction efficiency of a target substance into a cell, let alone in a liquid phase or on a solid support. Moreover, there is no suggestion that a composition comprising an anti-integrin receptor antibody would increase the introduction efficiency of genetic material into the cell. In contrast, Zou *et al.* teach the critical components for enhancing transfection efficiency of a cell depend on the particular lipid compositions used and not a composition as presently claimed (see Abstract of Zou *et al.*).

The Action alleges that the skilled artisan would find it *prima facie* obvious to complex the anti-B_1 integrin (CD29) monoclonal antibodies taught by Sugano *et al.* to the cationic liposome for gene delivery taught by Zou *et al.* because the addition of antibodies for targeting of liposomes and drug delivery was known. Applicants respectfully disagree.

Applicants respectfully submit that Sugano *et al.* merely demonstrate that liposomes that contain doxyrubicin and that are conjugated to anti-B_1 integrin antibodies are targeted to cells expressing B_1 integrins. Sugano *et al.* are silent with regard to a composition comprising an interaction substance that comprises an anti-integrin receptor antibody that enhances the introduction efficiency of a target substance into a cell, let alone in a liquid phase or on a solid support. Sugano *et al.* merely teach targeting of small cell lung carcinoma cells that

express B_1 integrin, with a liposome that would bind to B_1 integrin. In contrast to the reasoning supplied in the Action, the fact that Zou *et al.* teach the critical components for enhancing transfection efficiency depend on the particular lipid compositions used and not a composition as presently claimed, and Sugano *et al.*, merely teach targeting of a specific cell type to deliver a drug, a skilled artisan would not find it *prima facie* obvious to modify Zou *et al.* with an anti-integrin antibody as taught by Sugano merely because each of the components were independently known in the art. In fact, *KSR* expressly contradicts this reasoning. *See, KSR* at 4, 14.

That Action alleges that the skilled artisan would have been motivated to add the anti-B_1 integrin antibodies of Sugano *et al.* to the cationic liposome for gene delivery taught by Zou *et al.* in order to target the gene delivery to lung cancer cells and because Fortunati *et al.* specifically suggest targeting gene delivery to cells expressing B_1 integrin, such as tumors. Applicants respectfully disagree.

Applicants respectfully submit that Fortunati *et al.* have made and characterized a multi-domain protein, $(SPKR)_4$inv, that comprises DNA- and integrin-binding subunits of the *Yersinia pseudotuberculosis* invasin protein. The synthetic peptide is only active in transfection assays when complexed with a cationic lipid micelle or cationic polymer. Fortunati *et al.* teach that the $(SPKR)_4$inv protein is effective at increasing the transfection efficiency of a nucleic acid. Fortunati *et al.* are silent with regard to any teaching of compositions comprising any antibody, let alone an antibody that binds to integrin, wherein the composition enhances the introduction efficiency of a target substance into a cell, let alone in a liquid phase or on a solid support. Applicants respectfully submit that one having ordinary skill in the art would not be motivated by Fortunati *et al.*, who teach a protein that binds DNA and integrin, to include the anti-integrin receptor antibody of Sugano *et al.* in the liposome of Zou *et al.* because: 1) Fortunati *et al.* teach that the $(SPKR)_4$inv protein is effective at increasing the transfection efficiency of a nucleic acid; 2) Sugano *et al.* already teach a liposome conjugated to anti-integrin antibodies; and 3) Zou *et al.* teach that the lipid formulation is the critical parameter that enhances the transfection efficiency. The Action fails to provide a sufficient basis of rationale for the skilled to combine the references

as suggested in the Action merely because each of the components was independently known in the art. None of the references cited in the Action, either alone or in combination teach or suggest a rationale for deriving a composition comprising an interaction substance that comprises an anti-integrin antibody that enhances the introduction efficiency of genetic material into a cell, let alone in a liquid phase or on a solid support as presently claimed.

The Action concludes that one of ordinary skill in the art would have a reasonable expectation of success complexing the anti-B_1 integrin antibodies to the cationic liposome/DNA composition of Zou et al because methods of complexing the anti-B_1 integrin antibodies to liposomes are known, and Sugano *et al.* demonstrate successful complexing of anti-B_1 integrin antibodies to liposomes. Applicants respectfully disagree.

Zou *et al.* clearly teach that it is the particular lipid formulation that is the critical determinant for enhancing transfection and Sugano *et al.* merely teach liposomal targeting and are completely silent with regard to a composition that enhances the introduction of a genetic material into a cell. Thus, even if the skilled artisan combined the teachings of Zou *et al.* and Sugano *et al.*, there would be no reasonable expectation of success in arriving at a composition comprising an interaction substance that comprises an anti-integrin antibody that enhances the introduction efficiency of genetic material into a cell, let alone in a liquid phase or on a solid support as presently claimed.

Applicants respectfully submit that the OPTI-MEM® product insert and Kamata *et al.* fail to remedy the insufficiencies of the combination of Zou *et al.*, Sugano *et al.*, and Fortunati *et al.*

Thus, Applicants respectfully submit that the Action has failed to establish a *prima facie* case of obviousness against the presently claimed methods because it does not provide a clear articulation of why the skilled artisan would have any reasonable expectation of success in arriving at the presently claimed invention by combining Zou *et al.*, Sugano *et al.*, and Fortunati *et al.* in further view of the OPTI-MEM® product insert and Kamata *et al.*

Reconsideration and withdrawal of this basis of rejection are respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C. §103(A), SECOND REJECTION

Claims 20 and 21 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zou *et al.* (Cancer Gene Therapy, 2000, 7:683-696) in view of Fortunati *et al.* (Gene Therapy, 2000, 7: 1505-1515) and Sugano et al (Cancer Research, 2000, 60: 6942-6949), as evidenced by GIBCO product insert for OPTI-MEM® (Form No. 2017, June 2001, one page) and Kamata *et al.* (J of Biological Chemistry, 1994, 269, 26006-26010) as applied to claims 1, 4, 8, 11-18, 22, and 23 above, and further in view of Martin *et al.* (Gene Therapy and Molecular Biology, 1998, 1:173-214). Specifically, the Action alleges that Zou *et al.*, Fortunati *et al.*, and Sugano *et al.* teach as described above in the preceding obviousness rejection but collectively fail to teach a composition that comprises a gold colloidal particle. The Action relies on Martin *et al.* to remedy this insufficiency. The Action alleges that Martin *et al.* teach labeling liposomes with colloidal gold for purposes of visualizing their localization in vivo or in cells by electron microscopy and that liposomes are used for gene therapy of lung cancers and can be tagged with antibodies to target specific tissues.

Applicants respectfully traverse this basis for rejection and submit that the Action fails to establish a *prima* facie case of obviousness against claims 20 and 21 because the teachings of Martin *et al.* fail to remedy the insufficiencies of Zou *et al.*, Sugano *et al.*, Fortunati *et al.*, the OPTI-MEM® product insert, and Kamata *et al.* discussed above with reference to the obviousness rejection of claims 1, 4, 8, 11-18, 22, and 23. Accordingly, reconsideration and withdrawal of this basis of rejection are respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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